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DISCUSSED CLINICAL CASES

Treat-and-Extend: optimizing outcomes in the treatment of exudative age-related macular degeneration

Treat-and-Extend: otimização de desfechos no tratamento da degeneração macular relacionada à idade na forma neovascular

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KEYWORDS:

Angiogenesis inhibitors, Macular degeneration; Macular edema.

ABSTRACT

Intravitreal anti-VEGF therapy remains the first-line treatment for neovascular age-related macular degeneration, as clinical experience continues to mirror the positive outcomes reported in the FDA registration trials. Though some retina specialists remain trailing the treatment protocols specified in the trials, others have adjusted their regimens to achieve similar results with fewer injections. Treat-and-Extend acted as an approach of maintaining optimal visual acuity over the long term, keeping sensitive to the often-burdensome treatment schedules required.

PALAVRAS-CHAVE:

Inibidores da angiogênese; Degeneração macular; Edema macular.

RESUMO

A terapia com injeção intravítrea de anti-VEGF continua sendo o tratamento de primeira linha para a forma neovascular da degeneração macular relacionada à idade, pois a experiência clínica continua a refletir os resultados positivos relatados nos ensaios de registro na FDA. Embora alguns especialistas em retina continuem seguindo os protocolos de tratamento especificados nos ensaios, outros ajustaram seus esquemas para obter resultados semelhantes com menos injeções. O esquema *treat-and-extend* tem atuado como uma abordagem para manter a acuidade visual ideal no longo prazo, mantendo-se sensível aos cronogramas de tratamento muitas vezes onerosos que são necessários.

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy remains the first-line treatment for neovascular age-related macular degeneration [nAMD], consisting in an undeniable breakthrough at that time, with patients treated according to a fixed monthly regimen with gains of between 6.5 and 10 letters after 2 years of therapy[1-3].

However, the dilemma is translating rationally the outcomes of pivotal trials into the real world. Nevertheless, most of retina specialists understand that undertreatment is a major factor avoiding the best possible outcomes on our clinical practice. The demand for our patients presently is the pursuit for treatment plans that provide similar efficacy obtained with the fixed schedule, but with a burdenless appro-

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ach, including less visits, and fewer injections on a long-term basis. This demand incited that most retina specialists abandoned a fixed monthly dosing, and also consequential to different results achieved in our routine, diverse from those attained in the clinical trials.

PRN (pro re nata) or as-needed therapy presented itself as a promising regimen with similar gains that those accomplished with monthly injections, but offering a flexible, and more reactive approach, opposed to the extremely proactive fixed regimen. Though, PRN is still related to the burden of monthly monitoring, that might not grant timely treatment of recurrences, bringing undertreatment to light. To address unmet needs in nAMD, several strategies to reduce treatment load have being explored.

Evolving treatment strategies:

Ranibizumab 0.5 mg (Lucentis; Genentech) was the first approved intravitreal anti-VEGF for treatment of choroidal neovascularization (CNV) secondary to nAMD, based on monthly injections after an initial loading phase, according to the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration), and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) results, back in 2006[1,3]. Aflibercept (Eylia; Regeneron) followed it later, with patients receiving bimonthly injections after a similar upload dose[4].

The PrONTO study presented as a cornerstone to PRN treatment, demonstrating that an OCT-guided variable dosing regimen could sustain visual acuity comparable to those from the phase 3 trials with fewer intravitreal injections[1,4-7]. Although patients in strictly controlled clinical trials, such as HARBOR and CATT achieved gains of 8.2 and 6.8 letters, respectively, at 12 months, results with PRN regimens in patients with nAMD in clinical practice have often been disappointing, compared to real-world evidence, suggesting that the aftermath is less impressive in practice, with initial gains obtained still during the upload phase of three-monthly injections, and that might not be maintained for a durable period[8-10].

Furthermore, PRN regimen may allow the recurrence of angiographic leakage, and CNV growth. Multiple relapses can lead to a further progression of the disease, resulting in poor long-term outcomes. Until new therapies are approved, accumulating data support the extending of treatment intervals according to individual assessment of disease activity.

Treat-and-extend: optimizing results

This protocol involves monthly treatment with anti-VEGF until the macula through OCT is considered "dry" and with stable visual acuity. This concept comes along with the absence of subretinal fluid or intraretinal cysts, and the central retinal subfield thickness (CST) based on OCT is no greater than 2 standard deviations from the normal of the patterns used by commercially available devices. If the patient is considered "dry", and keeping stable vision, their interval until the next injection, regardless the drug employed, can be extended appropriately by a predetermined interval. While protocols vary, the interval between visits typically increases by 2 weeks, to a maximum 12 weeks period when there is no signs of present exudation or fluid, and decreases by 2 weeks, to a minimum of 4 weeks, if recurrent disease is detected on the OCT B-scans[11-16].

Studies comparing these regimens propose that fixed interval protocols are more effective than PRN. PRN protocols usually analyses patients injected on a monthly basis until neovascular activity has ceased or the physician believes that maximum improvement has been achieved. The criteria used to diagnose recurrent activity differ among studies but generally include the following: persistent or new subretinal or intraretinal fluid, new hemorrhage, macular thickening of at least 50 μm or 100 μm, decrease in vision of 5 ETDRS letters, and persistent neovascularization on fluorescein angiography. Once the longest injection interval that maintains a stable macula has been determined, the patient can be repeatedly treated for long periods of time, with reasonable assurance that disease activation or worsening will not occur between injections[9,11-14].

Treat-and-Extend dosing have the potential to match the results of fixed-interval treatments[4]. The procedure related is well known by most retinal specialists and became the most popular modality of anti-VEGF therapy in patients with nAMD, according to the American Society of Retina Specialists. Several studies, including the Lucentis Compared to Avastin Study (LUCAS), show that Treat-and-Extend acts as well as expected compared to a fixed monthly dosing interval. The LUCAS study was the first trial to investigate this treatment strategy with ranibizumab.

Patients (n=172) were given monthly injections until no signs of present activity, clinically assessed or guided by OCT images, followed by a Treat-and-Extend regimen for 24 months. If lesions were considered active (mostly according to presence of fluid on OCT, and new or persistent hemorrhage), a novel series of injections was given, and the interval until next treatment was reduced by 2 weeks to a minimum of 4 weeks. If lesions were considered inactive, the patient was treated, and the interval extended by 2 weeks to a maximum of 12 weeks. The results of LUCAS demonstrated for the 1st time that Treat-and-Extend regimen with ranibizumab could provide sustained visual acuity improvements over 2 years, with a mean change from baseline of 8.4 letters in Year 1 and 6.6 letters in Year 2, following a mean 8.0 injections (in both Year 1 and Year 2. More than three-fourths of U.S. retina specialists follow the strategy employed in LUCAS, as orientation to a Treat-and-Extend dosing regimen[10,17].

This strategy has taken off, including subsequent adjustment of labeled drugs for the treatment of nAMD. The approved dosing posology in Europe for ranibizumab was originally based on a personalized treatment schedule, although this has evolved over the past decade from the original label from 2007 which recommended administration according to a PRN regimen. Further update in 2014 removed the requirement for any vision loss and need for monthly visits as required parameters before retreatment. Injection is now recommended until maximum VA is achieved and/or there are no signs of disease activity, at which stage monitoring and treatment intervals should be determined by the physician based on disease activity, as evaluated by functional and anatomical parameters, most importantly OCT imaging. This increased flexibility allows a more proactive approach, if disease activity is noted, as well as extending monitoring intervals[7].

Despite the fact that an individualized and more proactive treatment, Treat-and-Extend dosing is variable. In some studies, the maximum extension interval is 8 weeks while in others it is 12. Therefore, there is still a lack of reliable clinical data for patients treat up to 3 years[17-22].

Herein, the authors address the management of nAMD with a Treat-and-Extend strategy, with emphasis on the results of most relevant clinical trials, and real-world experience, and further developments in individualized dosing for these patients, focusing the look for maximum intervals allowed with both already available, and promising therapies in a near future.

Most significant results with Treat-and-Extend

Several prospective and retrospective studies have been performed to investigate the efficacy and safety of Treat-and-Extend for the management of different retinal and choroidal disorders, specially nAMD, including 1-year data from TREND and TREX and studies carried out by Oubraham and Toalster, as well as 2 and 3-year data from the CANTREAT, TREX, ALTAIR, and RIVAL[15-17,23-25].

The TREND study was a 12-month, prospective, randomized, visual acuity assessor-masked, multicenter interventional study that evaluated both efficacy and safety of Treat-and-Extend with ranibizumab (n=323) compared with ranibizumab given according to a monthly regimen (n=327). At 12 months, the primary objective was met, demonstrating that Treat-and-Extend was statistically and clinically non-inferior to a monthly regimen, with approximately 2.5 fewer injections. The improvement in best corrected visual acuity (BCVA) from baseline was 6.2 letters in this arm, compared to 8.1 letters gain in the monthly arm (noninferiority, $p<0.001$). Patients in both treatment groups showed a rapid initial gain in BCVA that was sustained until the end of the study, and 62% of patients in the Treat-and-Extend arm achieved an injection interval of 8 weeks or more[16].

At 12 months in the TREX study, patients in the Treat-and-Extend group achieved and attained similar visual outcomes with fewer injections than those treated with monthly dosing (10.5 versus 9.2 letters at 12 months with 10.1 and 13.0 injections, respectively). At 24 months, these gains were sustained and were not significantly different between treatment arms ($p=0.64$; 8.7 letters in the Treat-and-Extend arm versus 10.5 letters in the monthly treatment group), with 7 fewer injections and clinic visits over 2 years (18.6 in the Treat-and-Extend arm versus 25.5 in the group treatment)[15].

The Canadian Treat-and-Extend Analysis Trial with Ranibizumab Study (CANTREAT) compared ranibizumab on a Treat-and-Extend basis with monthly dosing in treatment-naive patients (Treat-and-Extend, n=268; monthly, n=258). The primary outcome of noninferiority regarding visual acuity was met with mean BCVA improvement of 8.4 letters (SD, 11.9 letters) and 6.0 letters (SD, 11.9 letters; $p=0.017$) in the Treat-and-Extend and monthly regimens, respectively, with a between-group mean difference of 2.38 letters (95% CI 0.32-4.45 letters). Per protocol, a secondary analysis was performed to test superiority of number of injections received up to month 12, showing signifi-

cantly fewer injections with Treat-and-Extend versus monthly dosing (9.4 and 11.8 injections, respectively), with a mean difference of -2.46 injections (95% CI, -2.68 to -2.23 injections)[23].

RIVAL is the first randomized controlled trial to compare ranibizumab and aflibercept using a Treat-and-Extend regimen. BCVA gains were seen in both study arms. At 24 months, patients in the ranibizumab arm had achieved a mean 6.6 letter improvement, compared with 4.6 letters in the aflibercept arm (least-square means; p=0.15). Similar proportions of patients in each study arm achieved gains of at least 15 letters from baseline to month 24 (25% and 19% for ranibizumab and aflibercept, respectively) and there was no statistical difference between both groups in terms of mean change in CST from baseline to month 24 (p=0.23). There were no observed differences regarding the proportion of patients with no intra and or subretinal fluid at month 24 (57% and 61% for ranibizumab and aflibercept, respectively; p=0.62)[19].

The ALTAIR study, performed in Japan, was a post hoc analysis of the VIEW 1 and VIEW 2 studies of aflibercept. Patients were extended at either 2-week or 4-week intervals, with 42% to 50% of patients reaching a quarterly dosing interval during the 1st year of treatment. Both 2-week and 4-week extension groups had similar visual acuity outcomes. Data from the 2nd year are upcoming[21].

Development of macular atrophy during Treat-and-Extend treatment

Patients treated on a long-term basis with anti-VEGF injections usually present as a significant chronic effect, development or increased macular atrophy during treatment. It is present in virtually all eyes at this stage, and its progression over the late stage of these patients' course was associated with visual decline over this period.

The question about the guilty role has maintained unclear since ranibizumab approval by the FDA: should macular atrophy be considered part of natural history of a chronic disease, or multiple injections could play a major role on its birth? The actual function of VEGF suppression on development or progression of macular atrophy is not yet answered. SEVEN-UP augments concepts in a long-duration patient cohort, but the mechanisms of macular atrophy formation and progression in the setting of treated nAMD remain inconclusive. In one hypothesis, atrophy could be explained by the progression of underlying macular atrophy, as would have occurred in the absence of CNV formation, or perhaps accelerated by factors in the neovascular process. By the other hand, anti-VEGF itself has been proposed to promote macular atrophy, by counteracting the role of constitutively produced VEGF in neuronal or vascular maintenance[7].

The previously mentioned RIVAL study had as primary outcome to investigate whether there is a difference in the development of macular atrophy between ranibizumab and aflibercept when using a treat-and-extend regimen to treat the studied eye of patients with nAMD, with respect to growth in the area of macular atrophy over 24 months. Key secondary objectives included a comparison of the number of injections and changes in BCVA from baseline to month 12 and 24. This study enrolled 281 treatment-naïve eyes from 281 participants with active CNV secondary to nAMD, randomizing 142 to treatment with ranibizumab and 139 to aflibercept, given according to an identical Treat-and-Extend regimen, with three initial monthly injections and a maximum extension period of 12 weeks. Treatment intervals were based on disease activity, defined as a loss of VA of 5 or more letters, new retinal hemorrhage, or the presence of any intra or subretinal fluid on OCT[19]. Besides the RIVAL study, the AREDS2 report 16 analyzed the prevalence, incidence, and clinical characteristics of eyes with geographic atrophy (GA) in patients with nAMD, including clinical and genetic factors affecting enlargement. At baseline, 517 eyes (6.2%) of 411 participants (9.8%) had pre-existing GA (defined as absence of nAMD), with the following characteristics: 33% central, 67% noncentral; and the following configurations: 36% small, 26% solid unifocal, 24% multifocal, 9% horseshoe or ring-shaped, and 6% indeterminate. Of the remaining 6530 eyes at risk, 1099 eyes (17.3%) of 883 participants developed incident GA without prior neovascular disease during mean follow-up of 4.4 years. The Kaplan-Meier rate of incident GA was 19% of eyes at 5 years. In eyes with incident GA, 4-year risk of subsequent nAMD was 29%. In eyes with incident noncentral GA, the 4-year risk of central involvement was 57%. GA enlargement rate (following square root transformation) was similar in eyes with pre-existing GA (0.29 mm/year; 95% CI=0.27-0.30) and incident GA (0.28 mm/year; 95% CI=0.27-0.30). Its progression was significantly faster with noncentrally, multifocality, intermediate baseline size, and bilateral GA

(p<0.0001). Enlargement was significantly faster with ARMS2 risk (p<0.0001), C3 non-risk (p=0.0002), and APOE non-risk (p=0.001) genotypes[26,27].

DISCUSSION

Macular atrophy: At 24 months of RIVAL study, on the primary efficacy endpoint of mean change in square-root area of macular atrophy from baseline to month 24, there was no significant difference between ranibizumab (0.36 mm) and aflibercept (0.28 mm, p=0.24). It is interesting to consider these increases reported over 2 years in the light of data on the natural history of macular atrophy reported in the AREDS2 study, with enlargement rates of 0.29 mm and 0.28 mm per year reported for existing and emerging atrophy[27]. From baseline to month 24, the proportion of patients with macular atrophy in the RIVAL study increased from 7 to 37% for ranibizumab and from 6 to 32% for aflibercept[19,26,27].

It's certainly useful to have studies such as this to give us more detail about the atrophy risk, especially since the imaging, detection, and quantification of atrophy has progressed since early results such as those from the CATT study, which were based on color photographs alone. In contrast, the recent RIVAL study used autofluorescence and other types of multimodal imaging. However, RIVAL study shows that the different modalities for VEGF suppression within the eye do not appear to have different effects on macular atrophy development, but the actual role of VEGF suppression on macular atrophy is not yet answered. This is something that is worthy of further study, especially as longer-acting agents, which will suppress VEGF in the eye for a longer period of time, become available[1,6,11].

Some analysis of AREDS2 data on natural history of GA provide representative data on GA evolution and enlargement. GA enlargement, which was influenced by lesion features, was relentless, resulting in rapid central vision loss. The genetic variants associated with faster enlargement were partially distinct from those associated with risk of incident GA. These findings are relevant to further investigations of GA pathogenesis and clinical trial planning[26,27].

FLUID: First, all of the patients in FLUID received regular, ongoing anti-VEGF treatment regardless of fluid status. The current protocol did not allow for cessation of therapy under any circumstances. Although many prospective trials have used PRN algorithms, no large prospective trial conducted to date in the anti-VEGF era has intentionally withheld treatment for patients with nAMD with active IRF or SRF. Second, analyses of prior prospective nAMD data sets have identified baseline SRF as a good prognostic indicator. The 2-year FLUID study supports the hypothesis that some residual subfoveal SRF may be tolerated when using a Treat-and-Extend management approach, and continued indefinite monthly dosing is not necessarily mandated. Critical to clinical implementation, however, is that even patients' eyes in the relaxed arm of this study were required to demonstrate resolution of IRF before interval extension[7].

Finally, it is worth raising a cautionary note regarding the clinical implementation of a relaxed approach to clinical management of patients with nAMD. The majority of available clinical data indicate that real-world treatment frequencies in the management of patients with nAMD are substantially below those observed in prospective trials. As a result, clinical outcomes in the real world are also substantially lower than those achieved in most prospective trials. Therefore, achieving and maintaining a dry macula in the ongoing, long-term management of patients with nAMD in order to optimize global outcomes from this blinding disease should remain a priority.

It is reasonable to deal with nAMD, from a macro perspective, as a chronic disorder that with variable responses, and related unpredictable results.

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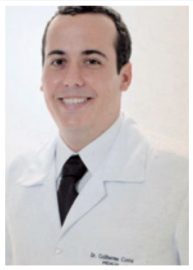
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